EXHIBIT A: MARKED VERSION OF AMENDED PARAGRAPHS IN THE SPECIFICATION
U.S. APPLICATION SERIAL NO. 09/724,538
(ATTORNEY DOCKET NO. 9301-123)

(as amended January 9, 2001)

On page 4, please amend the paragraph beginning "However, current DNA array technologies typically monitor the 3' ends", as follows:

However, current DNA array technologies typically monitor the 3' ends of mRNA molecules in a cell, rather than the expression levels of individual exons that make up the mRNAs. For example, probes used in cDNA arrays typically range in sizes from about 0.6 to 2.4kb (Duggan et al., *Nature Genetics* Supplement *21*:10-14), and are generally complementary to the 3' ends of the mRNA molecules. Probes used in cDNA arrays are biased to the 3' end because labeling methods typically rely on d(T) primed reverse transcription. Expression analysis using high density oligonucleotide arrays has been described that requires scoring and averaging of as many as 20 oligonucleotide probes on an array, chosen from various locations of the coding sequence of a gene, to determine the transcript level of the corresponding mRNA (see, *e.g.*, Lockhart *et al.*, 1996, *Nature Biotechnology 14*:1675; U.S. Patent Nos. 5,578,832; 5,556,752; 5,510,270; and 6,040,138; Lipshutz et al., 1999, *Nature Genetics* Supplement *21*:20-24). Again, these probes are placed near the 3' ends of mRNA molecules and the probe intensities are averaged to a single value, and thus does not provide information of the expression of individual exons across the genes. In addition, it has been found that the majority of splicing events [occurr] <u>occurs</u> in 5' untranslated regions, which leads to the generation of additional protein domains rather than alternating domains (Mironov et al., 1999, Genome Research 9:1288-1293). It has also been found that alternative exon-intron structures, i.e., with different end points, exist in many exons, which leads to expressed exons of different lengths (Mironov et al., 1999, Genome Research 9:1288-1293). Thus, there exists a need to design DNA arrays that measure the expression levels and the lengths of a plurality of exons for each of a plurality of genes in the genome of an organism. There exists a need for methods for quantitatively monitoring alternative splicing on a genome-wide scale.

On page 46, please amend the paragraph beginning "In preferred embodiments", as

follows:

In preferred embodiments, the target polynucleotides to be analyzed are prepared *in vitro* from nucleic acids extracted from cells. For example, in one embodiment, RNA is extracted from cells (*e.g.*, total cellular RNA, poly(A)$^+$ messenger RNA, fraction thereof) and messenger RNA is purified from the total extracted RNA. Methods for preparing total and poly(A)$^+$ RNA are well known in the art, and are described generally, *e.g.*, in Sambrook *et al.*, *supra*. In one embodiment, RNA is extracted from cells of the various types of interest in this invention using guanidinium thiocyanate lysis followed by CsCl centrifugation (Chirgwin *et al.*, 1979, *Biochemistry 18*:5294-5299). cDNA is then synthesized from the purified mRNA using, *e.g.*, oligo-dT or random primers. In preferred embodiments, the target polynucleotides are cRNA prepared from purified messenger RNA extracted from cells. As used herein, cRNA is defined here as RNA complementary to the source RNA. The extracted RNAs are amplified using a process in which doubled-stranded cDNAs are synthesized from the RNAs using a primer linked to an RNA polymerase promoter in a direction capable of directing transcription of anti-sense RNA. Anti-sense RNAs or cRNAs are then transcribed from the second strand of the double-stranded cDNAs using an RNA polymerase (see, *e.g.*, U.S. Patent Nos. 5,891,636, 5,716,785; 5,545,522 and 6,132,997; see also, U.S. Patent Application Serial No. 09/411,074, filed October 4, 1999 by Linsley and Schelter and U.S. Provisional Patent Application [Serial] No. [to be assigned, Attorney Docket No. 9301-124-888] 60/253,641, filed on November 28, 2000, by Ziman et al.). Both oligo-dT primers (U.S. Patent Nos. 5,545,522 and 6,132,997) or random primers (U.S. Provisional Patent Application Serial No. [to be assigned, Attorney Docket No. 9301-124-888] 60/253,641, filed on November 28, 2000, by Ziman et al.) that contain an RNA polymerase promoter or complement thereof can be used. Preferably, the target polynucleotides are short and/or fragmented polynucleotide molecules which are representative of the original nucleic acid population of the cell.

EXHIBIT B: CLEAN VERSION OF AMENDED PARAGRAPHS IN THE SPECIFICATION
U.S. APPLICATION SERIAL NO. 09/724,538
(ATTORNEY DOCKET NO. 9301-123)

(as amended January 9, 2001)

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On page 46, please replace the paragraph beginning "In preferred embodiments" with

the following paragraph:

In preferred embodiments, the target polynucleotides to be analyzed are prepared *in vitro* from nucleic acids extracted from cells. For example, in one embodiment, RNA is extracted from cells (*e.g.*, total cellular RNA, poly(A)$^+$ messenger RNA, fraction thereof) and messenger RNA is purified from the total extracted RNA. Methods for preparing total and poly(A)$^+$ RNA are well known in the art, and are described generally, *e.g.*, in Sambrook *et al.*, *supra*. In one embodiment, RNA is extracted from cells of the various types of interest in this invention using guanidinium thiocyanate lysis followed by CsCl centrifugation (Chirgwin *et al.*, 1979, *Biochemistry 18*:5294-5299). cDNA is then synthesized from the purified mRNA using, *e.g.*, oligo-dT or random primers. In preferred embodiments, the target polynucleotides are cRNA prepared from purified messenger RNA extracted from cells. As used herein, cRNA is defined here as RNA complementary to the source RNA. The extracted RNAs are amplified using a process in which doubled-stranded cDNAs are synthesized from the RNAs using a primer linked to an RNA polymerase promoter in a direction capable of directing transcription of anti-sense RNA. Anti-sense RNAs or cRNAs are then transcribed from the second strand of the double-stranded cDNAs using an RNA polymerase (see, *e.g.*, U.S. Patent Nos. 5,891,636, 5,716,785; 5,545,522 and 6,132,997; see also, U.S. Patent Application Serial No. 09/411,074, filed October 4, 1999 by Linsley and Schelter and U.S. Provisional Patent Application No. 60/253,641, filed on November 28, 2000, by Ziman et al.). Both oligo-dT primers (U.S. Patent Nos. 5,545,522 and 6,132,997) or random primers (U.S. Provisional Patent Application Serial No. 60/253,641, filed on November 28, 2000, by Ziman et al.) that contain an RNA polymerase promoter or complement thereof can be used. Preferably, the target polynucleotides are short and/or fragmented polynucleotide molecules which are representative of the original nucleic acid population of the cell.

EXHIBIT C: MARKED VERSION OF AMENDED CLAIMS
U.S. APPLICATION SERIAL NO. 09/724,538
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(as amended January 9, 2001)

10. (Amended) The method of claim 1, wherein said measuring is performed by a method comprising

(a) contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises a plurality of polynucleotide probes of different nucleotide sequences bound to different regions of a support, each of said different nucleotide sequences comprising a sequence complementary and hybridizable to a sequence in a different exon or multiexon of said cell sample; and

(b) measuring levels of hybridization between said probes and said RNAs or nucleic acids.

Claims 37-44 have been canceled.

45. (Amended) The method of claim 1[,] or 10, [37, or 38,] wherein said organism is a human.

46. (Amended) The method of claim 1[,] or 10, [37, or 38,] wherein said organism is a plant.

Claims 47-85 have been canceled.

86. (Amended) The method of claim 1[,] or 10, [47 or 83,] wherein said cell sample has been subjected to a perturbation.

Claims 91-156 have been canceled.

157. (Amended) The method of claim 1, wherein said measuring is performed by a method comprising

(a) contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises a plurality of polynucleotide probes of different nucleotide sequences bound to different regions of a support, each of said different nucleotide sequences comprising a sequence complementary and hybridizable to a sequence in a different exon or multiexon in the genome of an organism from which said cell sample is derived; and

(b) measuring levels of hybridization between said probes and said RNAs or nucleic acids.

182. (Amended) The method of claim [151 or] 157, wherein said expression levels are measured as continuous variables.

Claims 184-211 have been canceled.

212. (Amended) The method of claim 1[,] or 10, [37, 38, 47, 83 or 151,] wherein said organism is a fungus.

New claims 214-279 have been added.